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Case Report

Multimodal Assessment of Immunosuppressive Therapy in a Patient With Chronic Active Myocarditis 3 Months Following COVID-19 Infection

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Only limited evidence is available regarding the efficacy of immunosuppressive therapy for post–COVID-19 chronic active myocarditis. We present a case of a 28-year-old woman with post–COVID-19 virus–negative chronic active myocarditis. Immunosuppressive therapy improved the left ventricular ejection fraction from 21% to 42%, and ameliorated inflammatory activity as assessed by cardiac magnetic resonance imaging and endomyocardial biopsy. This report is the first to evaluate inflammatory activity before and after immunosuppressive therapy in post–COVID-19 virus–negative chronic active myocarditis using both endomyocardial biopsy and cardiac magnetic resonance imaging.

Novel Teaching Points

- CMR might be useful for assessing inflammatory activity in post–COVID-19 virus–negative chronic active myocarditis.
- Immunosuppressive therapy might be a viable treatment option for post–COVID-19 virus–negative chronic active myocarditis.

Case

A 28-year-old female patient without notable medical history presented with a chief complaint of chest pain, 3 months after having a mild case of COVID-19 infection. After admission, she developed pulseless ventricular tachycardia but responded well to conservative treatment. Acute lymphocytic myocarditis was diagnosed based on endomyocardial biopsy (EMB) findings. Cardiac magnetic resonance (CMR) was not performed because the diagnosis of lymphocytic myocarditis was established unequivocally by myocardial biopsy. No medications had been newly initiated, and blood sample analyses revealed no abnormalities indicative of systemic inflammatory disorders. She was discharged 24 days after admission, with a troponin I level of 0.004 ng/mL and a left ventricular ejection fraction (LVEF) of 42% on transthoracic echocardiography (TTE).

One year later, she was readmitted due to dyspnea. TTE revealed a LVEF of 42% (Video 1, view video online), and blood tests showed an elevated troponin T level of 102 ng/mL (normal: < 16 ng/mL), an angiotensin-converting enzyme level of 5.2 U/L (normal: 8.3-21.4 ng/mL), and a soluble interleukin-2 receptor level of 290 U/mL (normal: < 613 ng/mL). CMR revealed late gadolinium enhancement in the subendocardial lesion of the entire left ventricle (Fig, 1A). CMR also revealed native T1 of approximately 1425 ms (normal: < 1300 ms), a native T2 ranging from 59 to 62 ms (normal: < 49 ms), and an extracellular volume (ECV) of approximately 40% (normal: < 35.2%), indicating myocardial edema and nonischemic myocardial injury (Fig. 1, B and C; Video 2, view video online).

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See page 829 for disclosure information.

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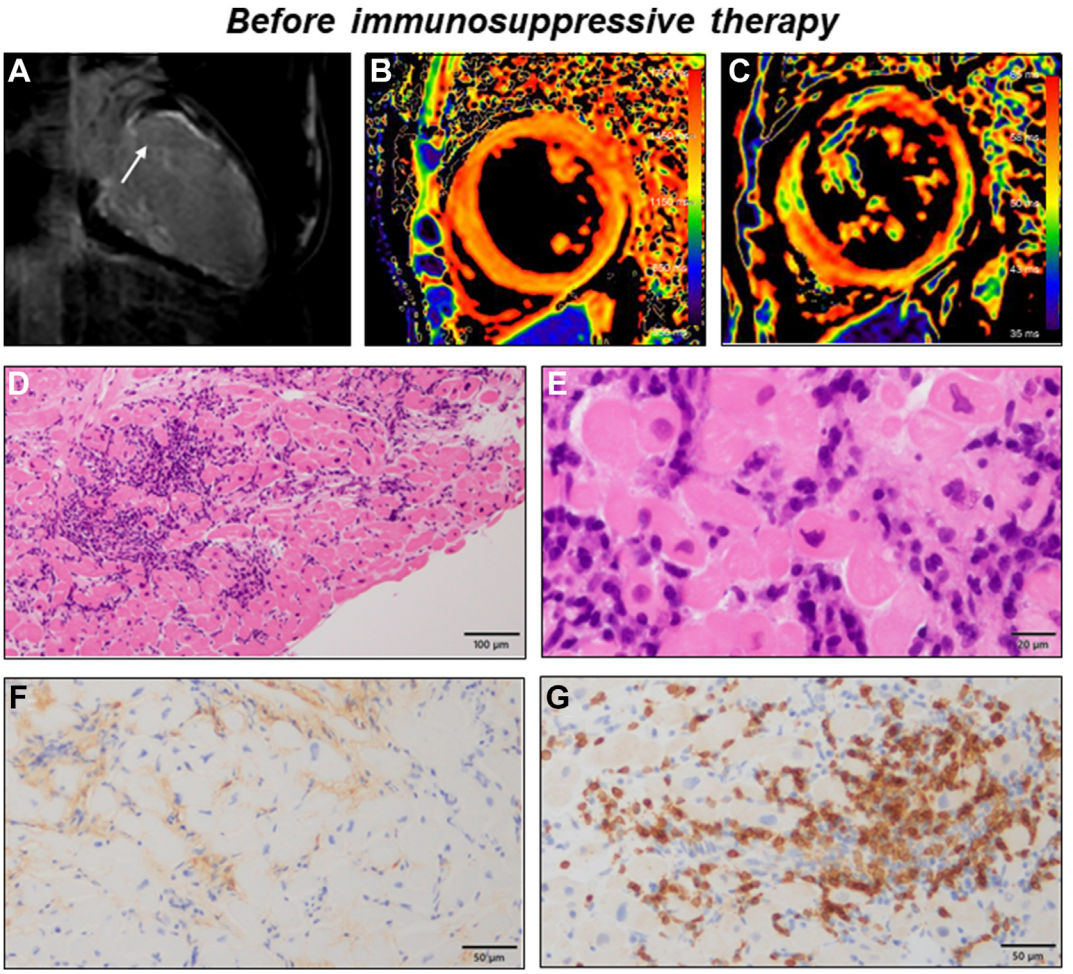

Figure 1. Cardiac magnetic resonance (CMR) imaging and histopathologic findings, preinitiation of immunosuppressive therapy. (**A**) CMR; subendocardial late gadolinium enhancement (**arrow**) in the entire left ventricle. (**B**) CMR; high signal intensity in the entire left ventricle on T1 mapping. (**C**) CMR; high signal intensity in the entire left ventricle on T2 mapping. (**D**) Hematoxylin and eosin staining; severe lymphocytic infiltration. (**E**) High-power field of hematoxylin and eosin staining; degeneration with inflammatory cell encroachment around cardiomyocytes. (**F**) Immunohistologic staining; positive Tenascin-C in the endocardium and interstitium. (**G**) Immunohistologic staining; severe CD3-positive T-cell infiltration in the endocardium and interstitium.

^{18}F-fluorideoxyglucose in positron emission tomography / computed tomography (FDG-PET CT) showed no substantial ^{18}F-fluorideoxyglucose uptake. EMB findings showed lymphocytic infiltration, myocardial damage, substantial infiltration of CD3-positive T cells, absence of eosinophils, and positive tenascin-C immunostaining in myocardial tissue. Based on these findings, we diagnosed chronic active myocarditis (Fig. 1, D-G). Cardiotropic virus testing using quantitative real-time polymerase chain reaction with the Quick-DNA/RNA FFPE Miniprep Kit (ZYMO RESEARCH, Orange, CA) did not detect any significant pathogenic viruses, including severe acute respiratory syndrome coronavirus 2, in the myocardial specimens. She was administered carvedilol at a dosage of 2.5 mg, and enalapril at 1.25 mg. Titrating the dose of carvedilol and enalapril, along with the initiation of mineralocorticoid receptor antagonist and sodium-glucose cotransporter 2 inhibitor, proved challenging due to the emergence of symptomatic hypotension and anorexia. Immunotherapy was not initiated, as the patient declined treatment due to concerns about potential side effects.

Three months later, her shortness of breath had worsened; blood tests showed a troponin T level of 86 ng/mL, and an LVEF further decreased to 21% (Video 3, view video online). Finally, she agreed to initiate immunosuppressive therapy and began oral treatment with prednisolone at a dose of 30 mg/d. One month after initiation of prednisolone, blood tests showed a decreased troponin T level of 7 ng/mL, and TTE revealed an improved LVEF of 45% (Video 4, view video online). Furthermore, the findings on CMR had improved (native T1 of 1290-1320 ms; native T2 ranging from 46 to 52 ms; ECV of approximately 35%), although the area of late gadolinium enhancement was unchanged (Fig. 2, A-C; Video 5, view video online). EMB showed decreased inflammatory cell infiltration, CD3-positive T cells, and the absence of myocardial injury (Fig. 2, D-G). Based on these findings, we have decided to extend the duration of steroid treatment and proceed with a tapering

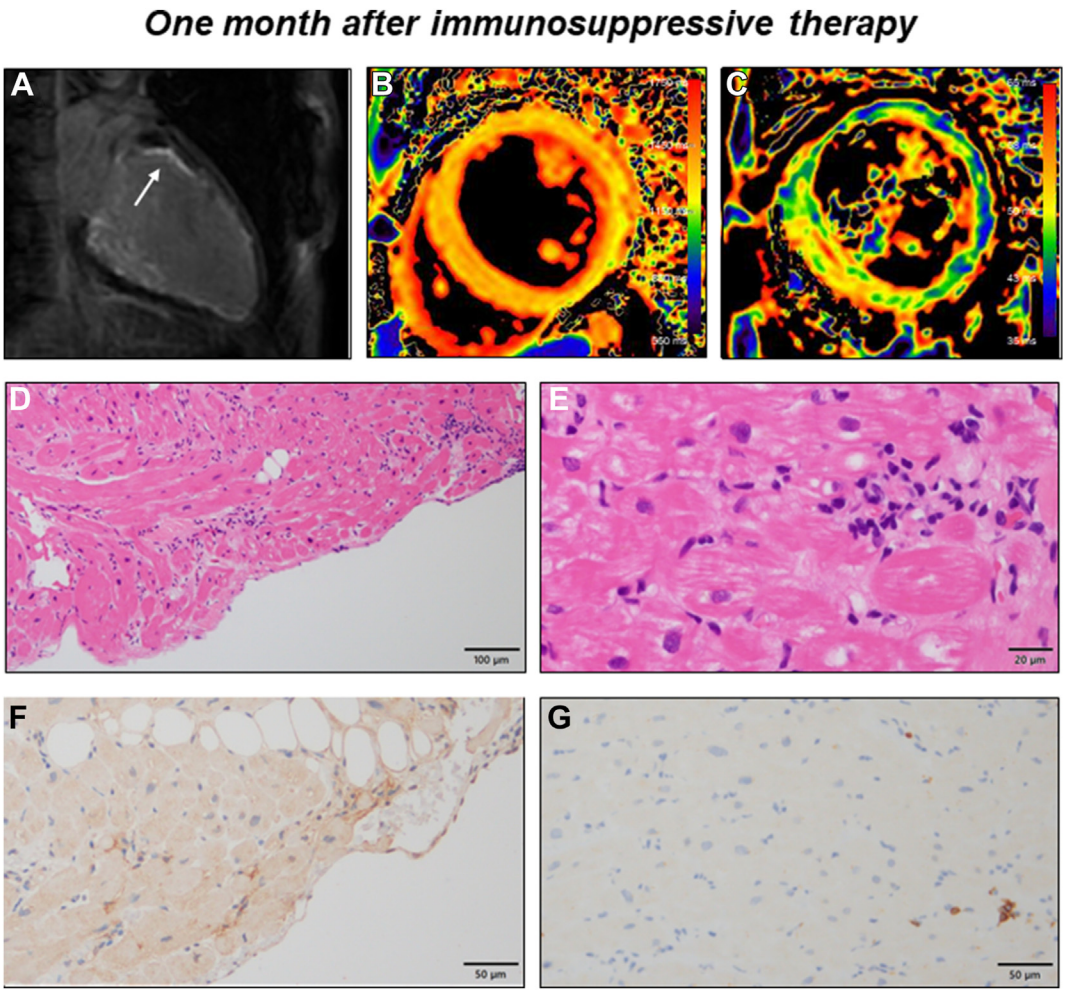

Figure 2. Cardiac magnetic resonance (CMR) and histopathologic findings, postinitiation of immunosuppressive therapy. (**A**) CMR; no significant change in late gadolinium enhancement area (**arrow**), compared to the level preinitiation of immunosuppressive therapy. (**B**) CMR; decreased signal intensity on T1 mapping, compared to the intensity preinitiation of immunosuppressive therapy. (**C**) CMR; decreased signal intensity on T2 mapping, compared to the intensity preinitiation of immunosuppressive therapy. (**D**) Hematoxylin and eosin staining; decreased cellular infiltration. € High-power field of hematoxylin and eosin staining; disappearance of degeneration and inflammatory cell encroachment. (**F**) Immunohistologic staining; positive Tenascin-C staining. (**G**) Immunohistologic staining; significant decrease in CD3-positive T-cell infiltration, compared to the level pre-initiation of immunosuppressive therapy.

approach, given the persistence of minimal residual myocardial edema.

Discussion

Ammirati et al. defined chronic myocarditis in an expert consensus document as a condition that is an intermediate stage between acute myocarditis and chronic inflammatory cardiomyopathy in patients with persistent myocardial inflammation.[1] Recently, the Japanese Circulation Society guideline defined chronic active myocarditis as myocardial inflammation lasting for at least 30 days, accompanied by cardiomyocyte injury, including myocardial necrosis or degeneration.[2] Only limited evidence has been gathered on the effectiveness of immunosuppressive therapy for chronic active myocarditis. However, the **T**ailored **Im**munosuppression in Virus-Negative **I**nflammatory **C**ardiomyopathy (TIMIC) trial demonstrated that immunosuppressive therapy improves LVEF and may reduce the risk of cardiac death in patients with chronic myocarditis.[3] Additionally, several studies have reported that immunosuppressive therapy may be beneficial for COVID-19-associated myocarditis.[4] In this particular case, virus-negative, chronic lymphocytic myocarditis developed 3 months post—COVID-19 infection. The immunosuppressive therapy led to decreased troponin levels, improved the LVEF, and yielded positive findings on CMR and histopathology. This result suggests that immunosuppressive therapy might be beneficial for virus-negative, chronic lymphocytic myocarditis precipitated 3 months post—COVID-19 infection.

CMR is a useful diagnostic tool for myocarditis, with T1/T2 mapping and ECV being particularly emphasized for assessing myocardial injury and edema.[5] Native T1 and ECV increase as a reflection of myocardial edema, necrosis, and fibrosis. Native T2 is elevated specifically in the presence of myocardial edema. However, whether CMR is available for monitoring inflammatory activity before and after immunosuppressive therapy for

chronic active myocarditis is poorly documented. Moreover, only limited data have been gathered on the potential usefulness of CMR in post-COVID-19 myocarditis.[4] In our case, CMR showed significant reduction in native T1, native T2, and ECV following the initiation of immunosuppressive therapy. These changes on CMR could reflect the disappearance of myocardial injury and the improvement of myocardial edema, consistent with the histopathologic findings.

To the best of our knowledge, this report is the first to evaluate inflammatory activity before and after immunosuppressive therapy in post—COVID-19 virus—negative chronic active myocarditis using both EMB and CMR. Although ascertainment of whether COVID-19 was causative for myocarditis in the present case is challenging, due to the absence of polymerase chain reaction testing on the initial myocardial specimen, instances of myocarditis manifesting at up to 18 months following COVID-19 infection have been documented. Consequently, chronic active myocarditis plausibly could develop subsequent to COVID-19 infection. Assessing inflammatory activity by CMR, using T1/T2 mapping and ECV, might be useful in treating post—COVID-19 virus—negative chronic active myocarditis. Further studies are warranted to investigate the applicability of CMR for assessing inflammatory activity in post—COVID-19 virus—negative chronic active myocarditis.

Ethics Statement

The research reported has adhered to relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective case report using de-identified data; therefore the IRB did not require consent from the patient.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2024.03.010.